UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte CHARLES W. RITTERSHAUS
and LAWRENCE J. THOMAS

Appeal No. 2005-2382
Application No. 09/943,334

HEARD November 17, 2005

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of treating atherosclerosis by administering a peptide comprising part of the cholesteryl ester transfer protein. The examiner has rejected the claims as nonenabled, inadequately described, and obvious. We have jurisdiction under 35 U.S.C. § 134. We reverse all of the rejections.

Background

"Cholesterol circulates through the body predominantly as components [[sic]] of lipoprotein particles (lipoproteins)," among which are high density lipoproteins (HDL), low density lipoproteins (LDL), and very low density lipoproteins (VLDL). Specification, page 1. "Cholesteryl ester transport protein (CETP) mediates the transfer of cholesteryl

esters from HDL to TG-rich [triglyceride-rich] lipoproteins such as VLDL and LDL, and also the reciprocal exchange of TG from VLDL to HDL." Page 2. "A high CETP cholesteryl ester transfer activity has been correlated with increased levels of LDL-associated cholesterol and VLDL-associated cholesterol, which in turn are correlated with increased risk of cardiovascular disease." Id.

The specification discloses "vaccine peptides [that] comprise a helper T cell epitope portion comprising a 'universal' or 'broad range' immunogenic helper T cell epitope, linked . . . to a B cell epitope portion comprising one or more B cell epitopes from CETP, such as found in the carboxyl terminal portion of human CETP protein that is involved in neutral lipid binding. . . . Other B cell epitopes from CETP may also be used." Pages 5-6. The specification states that such peptides, "when administered to a mammal, raise an antibody response against the mammal's own endogenous CETP thereby promoting a prophylactic or therapeutic effect against cardiovascular disease, such as atherosclerosis." Page 5.

Discussion

1. Claim construction

Claims 28, 29, and 37-39 are pending and stand rejected. Claim 28 is representative and reads as follows:

> 28. A method for treating or preventing atherosclerosis in a human or animal comprising administering to said human or animal an antigenic vaccine peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises a B cell epitope of CETP.

Thus, claim 28 is directed to a method of either treating or preventing atherosclerosis by administering to a mammal a peptide comprising a universal helper T cell epitope linked to a B cell epitope from cholesteryl ester transfer protein (CETP).

2. Enablement

The examiner rejected claims 28, 29, and 37-39 under 35 U.S.C. § 112, first paragraph, on the basis that "the specification, while being enabling for a method for treating atherosclerosis," does not enable a method of preventing atherosclerosis. Examiner's Answer, page 4. The examiner reasoned that "the burden of enabling the prevention of a disease (i.e.[,] the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition." Id., page 5. The examiner stated that the specification does not provide guidance regarding how to screen people for susceptibility to atherosclerosis and does not disclose a "specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing atherosclerosis." Id.

The examiner has not made out a prima facie case of nonenablement. In a nutshell, the examiner's basis for rejecting the claims is that the specification has not shown that the claimed method works to prevent atherosclerosis. The initial burden of proof, however, is on the examiner. See In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971): "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first

paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support" (emphasis in original). See also In re Armbruster, 512 F.2d 676, 678, 185 USPQ 152, 153 (CCPA 1975) ("Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct.").

Here, the specification states that the disclosed method is effective for treating or preventing atherosclerosis. See, e.g., page 1, lines 9-11 ("[T]his invention provides . . . methods . . . to treat cardiovascular disease prophylactically or therapeutically."). The burden of proof is therefore on the examiner to show reason to doubt the truth of this statement. The only evidence relied on by the examiner is Maillard,[1] which the examiner characterizes as stating that "there is a lack of effective methods capable of preventing atherosclerosis-related conditions. (see Abstract in particular)." Examiner's Answer, page 5.

Maillard does not support the examiner's position. Maillard relates to using vascular endothelial growth factor (VEGF) for treating ischemic heart disease. The reference says nothing that would cast doubt on the effectiveness of preventing atherosclerosis by inhibiting CETP. The passage that the examiner appears to be focused on relates to the "lack of effective treatment" for preventing leg amputations necessitated by atherosclerosis-related ischemia, not preventing atherosclerosis itself.

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[1] Maillard et al., "Contribution to gene therapy by VEGF," La Presse Medicale, Vol. 29, pp. 1731-1737 (2000).

The examiner has not met the initial burden of showing that undue experimentation would have been required to practice the claimed method. The rejection for lack of enablement is reversed.

3. Description

The examiner rejected claims 28 and 29 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description in the specification. The examiner acknowledged that the specification adequately describes "a method for treating or preventing atherosclerosis, comprising administ[er]ing an antigenic vaccine peptide . . . comprising a universal helper T cell epitope portion linked to B cell [sic, a B cell epitope portion?] of the a [sic] carboxyl [sic, carboxy] terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1." Examiner's Answer, page 6.

The examiner rejected claims 28 and 29, however, on the basis that the specification does not adequately describe "a method for preventing atherosclerosis comprising administ[er]ing vaccine peptide comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP." Id. (emphasis in original). The examiner's reasoning in support of this conclusion was that

> there is no described or art-recognized correlation or relationship between the structure of the invention [(]a vaccine peptide comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP[)] and production of native antibodies that recognize the subject's own, endogenous CETP, the feature deemed essential to the instant invention.

Examiner's Answer, page 7.

We agree with the examiner that describing a claimed method requires describing the products needed to carry out the method. See University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 926, 69 USPQ2d 1886, 1894 (Fed. Cir. 2004) ("Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.").

However, we disagree with the examiner's application of the relevant legal standard to the facts of this case. The Court of Appeals for the Federal Circuit has adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (emphasis omitted, bracketed material in original).

In this case, the claimed method requires use of a compound comprising a universal helper T cell epitope linked to a B cell epitope portion of CETP. The examiner has objected only to the specification's description of B cell epitope portions of CETP.

The specification describes the complete sequence (primary structure) of CETP (SEQ ID NO:4), which will necessarily include any portions that include a B cell epitope. The specification also describes "two B cell epitopes of human CETP; i.e., amino acids

349 to 367 and amino acids 461 to 476 of the amino acid sequence for mature human CETP (SEQ ID NO:4)." Page 7, lines 11-13.

Finally, the specification includes a plot of the antigenic index of human CETP (page 9, lines 3-5, and Figure 8A). The specification discloses that "by combining analyses of plots of hydrophilicity, surface probability, amphilic [sic] helix, amphiphilic sheets and secondary structure (Figures 8A and 8B), an Antigenic Index (see Figure 8A) of the entire protein's amino acid sequence can be derived leading to identification of B cell epitopes potentially useful in the vaccine peptides of this invention." Page 16, lines 2-6. The record also shows that methods of mapping antibody-binding epitopes in CETP were well known in the art. See Swenson, pages 14319-14320 (section headed "Localization of the Epitope of Monoclonal Antibodies TP2 and TP6").

Thus, the specification describes two exemplary CETP fragments that comprise B-cell epitopes as well as the complete sequence of CETP, which includes all of the portions of CETP that comprise a B-cell epitope; the specification also discloses the antigenic index of CETP, which shows those skilled in the art where epitopes are likely to be; and methods were known in the art for determining whether a given fragment of CETP comprises an epitope.

"A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses." Utter v. Hiraga, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988). Section 112, as interpreted by the courts, "require[s] only sufficient description to show one of skill in the [relevant] art that the inventor possessed the

claimed invention at the time of filing." Union Oil Co. of California v. Atlantic Richfield Co., 208 F.3d 989, 997, 54 USPQ2d 1227, 1233 (Fed. Cir. 2000).

The examiner has not adequately explained why, in view of the specification's disclosure, a person of ordinary skill in the art would not have considered Appellants to have been in possession of the claimed method at the time this application was filed. The rejection for lack of adequate written description is reversed.

3. Obviousness

The examiner rejected claims 28, 29, 37, and 38 under 35 U.S.C. § 103 on the basis that the claimed method would have been obvious in view of Whitlock,[2] "the known fact disclosed in the specification at page 2, lines 10-12,"[3] Stevens,[4] Swenson,[5] and Valmori.[6] See the Examiner's Answer, page 8.

The examiner cited Whitlock for its "teach[ing] that in vivo administration of CETP neutralizing antibodies leads to an elevation of circulating HDL [and] elevation in the ratio of circulating HDL to LDL." Examiner's Answer, page 9.[7] The examiner cited the instant specification as "disclos[ing] that it is well known that increased levels of

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[2] Whitlock et al., "Monoclonal antibody inhibition of cholesteryl ester transfer protein activity in the rabbit," J. Clin. Invest., Vol. 84, pp. 129-137 (1989).

[3] Lines 10-13 on page 2 of the specification read as follows: "Decreased susceptibility to cardiovascular disease, such as atherosclerosis, is generally correlated with increased absolute levels of circulating HDL and also increased levels of HDL relative to circulating levels of lower density lipoproteins such as VLDL and LDL."

[4] Stevens, U.S. Patent 6,143,305, issued November 7, 2000 (application filed June 6, 1995).

[5] Swenson et al., "Mechanism of cholesteryl ester transfer protein inhibition by a neutralizing monoclonal antibody and mapping of the monoclonal antibody epitope," J. Biol. Chem., Vol. 264, pp. 14318-14326 (1989).

[6] Valmori et al., "Use of human universally antigenic tetanus toxin T cell epitopes as carriers for human vaccination," J. Immunol., Vol. 149, pp. 717-721 (1992).

[7] The examiner also characterized Whitlock as "teach[ing] that an increased [sic] of HDL with a decreased [sic] of VLDL would lead to a decreased [sic] of LDL levels which would be beneficial for a decrease in the development of atherosclerosis." Examiner's Answer, page 9, citing "entire document and page 129 in particular." We have reviewed Whitlock, and particularly page 129, and have been unable to find support for the teaching asserted by the examiner. We have not, in fact, found any reference to "atherosclerosis"

circulating HDL is essential in therapeutically treating of atherosclerosis." Examiner's Answer, page 9.

According to the examiner, the claimed method "differs from the prior art by the recitation of using a vaccine peptide (i.e.[,] active immunization) . . . instead of using CETP neutralizing antibodies (i.e.[,] passive immunization) in a method for therapeutically treating atherosclerosis." Id. He relied on Swenson, Stevens, and Valmori to make up this difference. The examiner cited Swenson as teaching that a peptide made up of the C-terminal 26 amino acids of CETP contains a B-cell epitope and results in antibodies that neutralize CETP activity, as well as for allegedly teaching that "treating of atherosclerosis in human can be generally achieved by modulating the activity of endogenous CETP." Id.

The examiner relied on Valmori for its disclosure of universal T-cell epitopes derived from tetanus toxoid (id., page 10) and on Stevens for its disclosure that active immunization has advantages over passive immunization (id.). He concluded that the references would have made the instantly claimed method obvious because

> administration of [a] vaccine peptide [made up of a tetanus toxoid T cell epitope and the C-terminal 26 amino acids of CETP] would induce the generation of neutralizing antibody which would inhibit CETP activity (as taught by Whitlock et al.,) and inhibition of CETP activity would be essential in treating atherosclerosis (as taught by Whitlock et al., the known fact disclosed in the specification on page 2 and Swenson et al[.]).
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> . . . Inhibition of CETP activity would have been expected to be useful in therapeutically treating atherosclerosis as taught by Whitlock et al., the known fact disclosed in specification on page 2 and Swenson et al.

Examiner's Answer, page 11.

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in Whitlock. Therefore, we decline to credit Whitlock with the teaching asserted by the examiner.

Appellants argue that the cited references do not provide adequate motivation to combine their teachings or a reasonable expectation of successfully treating atherosclerosis. See, e.g., the Appeal Brief, pages 33-35.

We agree with Appellants that the references cited by the examiner do not support a prima facie case of obviousness. "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) (citations omitted).

In this case, we agree with Appellants that the cited references – viewed without the benefit of the instant disclosure – would not have suggested a method for treating or preventing atherosclerosis by administering a vaccine peptide made up of parts of CETP and tetanus toxoid. In particular, none of the references suggest that inhibiting CETP activity in vivo would be a promising approach to treating or preventing atherosclerosis. The examiner relies on Swenson and the instant specification as sources of motivation, but neither source supports the weight the examiner puts on it.

The examiner has characterized the instant specification as "disclos[ing] that it is well known that increased levels of circulating HDL is essential in therapeutically treating of atherosclerosis." Examiner's Answer, page 9. The cited passage reads as follows: "Decreased susceptibility to cardiovascular disease, such as atherosclerosis, is generally correlated with increased absolute levels of circulating HDL and also

increased levels of HDL relative to circulating levels of lower density lipoproteins such as VLDL and HDL" (emphasis added).

As is well known in this art, however, correlation is not causation. That is, the fact that increased levels of HDL are correlated with decreased susceptibility to atherosclerosis does not necessarily mean that those increased levels cause the decreased risk, such that artificially increasing HDL levels would result in decreased risk of atherosclerosis. Thus, the fact that increased HDL correlates with decreased risk of atherosclerosis would not provide a person of ordinary skill in the art a reasonable expectation that raising HDL levels would successfully treat atherosclerosis.

The examiner also relies on Swenson, which he characterized as teaching that "treating of atherosclerosis in human can be generally achieved by modulating the activity of endogenous CETP." Examiner's Answer, page 9. Again, however, the examiner has overstated the relevance of Swenson to the presently claimed method.

Swenson states that "CETP appears to play a role in the regulation of HDL-cholesteryl ester levels in rabbits and humans. Since HDL levels are inversely correlated with atherosclerosis in humans, the activity of CETP could have an important influence on atherosclerosis." The disclosure that CETP activity "could have an important influence on atherosclerosis" is too vague to provide those skilled in the art with motivation to seek to inhibit CETP in vivo as a way to treat or prevent atherosclerosis. See In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999): "[E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. . . . The range

of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" (citations omitted).

In addition, the cited references lack an adequate basis for a reasonable expectation of success. The examiner reasoned that Stevens, Valmori, Whitlock, and Swenson would have led those skilled in the art to expect that active immunization against CETP would have resulted in vivo in lower CETP activity and an increase in HDL. Examiner's Answer, pages 10-11. Therefore, he concluded, in view of the "known fact disclosed in the specification on page 2 that increase in the level of circulating HDL is essential in therapeutically treating of atherosclerosis, one [of] ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to therapeutically treat atherosclerosis" via the claimed method. Id., page 11.

As discussed above, however, the specification does not say that an increased HDL level "is essential in therapeutically treating . . . atherosclerosis." It simply says that decreased susceptibility to atherosclerosis is generally correlated with increased HDL level. For the reasons already discussed, the empirically observed correlation between increased HDL and decreased susceptibility is inadequate to lead a person of ordinary skill in the art to expect that a treatment that artificially increases HDL levels would successfully treat atherosclerosis.

The cited references may well have made it obvious to try to increase HDL by inhibiting CETP in vivo. "An 'obvious-to-try' situation exists when a general disclosure

may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." In re Eli Lilly & Co., 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). However, "'obvious to try' is not the standard under § 103." In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

Because the cited references would not have led a person of ordinary skill in the art to combine their respective teachings with a reasonable expectation of successfully treating atherosclerosis, they do not support a prima facie case of obviousness. The rejection of claims 28, 29, 37, and 38 under 35 U.S.C. § 103 is reversed.

The examiner also rejected claim 39 as obvious in view of Whitlock, "the known fact disclosed in the specification," Stevens, Swenson, Valmori, and Talwar.[8] This rejection suffers from the same deficiency discussed above, since the examiner cited Talwar only as a basis for making a dimerized vaccine peptide. The rejection of claim 39 is also reversed.

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[8] Talwar et al., "A vaccine that prevents pregnancy in women," Proc. Natl. Acad. Sci. USA, Vol. 91, pp. 8532-8536 (1994).

Summary

The examiner has not shown that the specification is nonenabling or fails to adequately describe the claimed method, and the cited references do not support a prima facie case of obviousness. The rejections on appeal are reversed.

REVERSED

Demetra J. Mills)
Administrative Patent Judge)
)

) BOARD OF PATENT
Eric Grimes)
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